

PCT

FC24 PTO-1390(modified) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE
(REV 10-95)ATTORNEY'S DOCKET NUMBER
01/22078TRANSMITTAL LETTER TO THE UNITED STATES
DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING

U.S. APPLICATION NO. (IF KNOWN), SEE 37 CFR

09/856798MAY 25 2001
PCT FILING UNDER 35 U.S.C., 371INTERNATIONAL APPLICATION NO.
PCT/US99/26094INTERNATIONAL FILING DATE
04 November 1999PRIORITY DATE CLAIMED
27 November 1998

TITLE OF INVENTION

Interferon Gamma Inducing Factor Based Vaccine And Use Of Same For Protective Immunity Against Multiple Sclerosis

APPLICANT(S) FOR DO/EO/US

Nathan KARIN; Gizi WILDBAUM

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(3)(2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ A translation of the International Application into English (35 U.S.C. 371(3)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☐ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19(35 U.S.C. 371(c)(3)).
10. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
11. ☐ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 13 to 18 below concern document(s) of information included:

13. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☒ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☐ A FIRST preliminary amendment.
A SECOND or SUBSEQUENT preliminary amendment.
16. ☐ A substitute specification.
17. ☐ A change of power of attorney and/or address letter.
18. ☐ Certificate of Mailing by Express Mail
19. ☒ Other items or information: *Letter re Name*

U.S. APPLICATION NO. (IF KNOWN), See 37 CFR <div style="font-size: 1.5em; font-weight: bold; margin-left: 100px;">097/856798</div>		INTERNATIONAL APPLICATION NO. PCT/US99/26094		ATTORNEY'S DOCKET NUMBER <div style="font-weight: bold;">01/22078</div>	
20. The following fees are submitted: BASIC NATIONAL FEE (37 CFR 1.492(a) (1) - (5)): <div style="display: flex; justify-content: space-between;"> <div> <input type="checkbox"/> Search Report has been prepared by the EPO or JPO <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1,482) <input type="checkbox"/> No international preliminary examination fee paid to USPTO (37 CFR 1,482) but international search fee paid to USPTO (37 CFR 1,445(a)(2)) <input type="checkbox"/> Neither international preliminary examination fee (37 CFR 1,482) nor international search fee (37 CFR 1,445(a)(2)) paid to USPTO <input type="checkbox"/> International preliminary examination fee paid to USPTO (37 CFR 1,482) and all claims satisfied provisions of PCT Article 33(2)-(4) </div> <div style="text-align: right;"> \$ 860 \$ 690 \$ 710 \$ 1000 \$ 100 </div> </div>				CALCULATIONS PTO USE ONLY 	
ENTER APPROPRIATE BASIC FEE AMOUNT =				\$ 690.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e))				\$.00	
CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	\$.00	
Total claims	34 - 20 =	14	14 x \$ 18	\$ 252.00	
Independent claims	10 - 3 =	7	7 x \$ 80	\$ 560.00	
Multiple Dependent Claims (check if applicable) <input type="checkbox"/>				\$.00	
TOTAL OF ABOVE CALCULATIONS =				\$ 1,502.00	
Reduction of 1/2 for filing by small entity, if applicable. <input checked="" type="checkbox"/>				\$ 751.00	
SUBTOTAL =				\$ 751.00	
Processing fee of \$130.00 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))				\$.00	
TOTAL NATIONAL FEE =				\$ 751.00	
Fee for recording the enclosed assignment (37 CFR 1.2(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) (check if applicable) <input checked="" type="checkbox"/>				\$ 40.00	
TOTAL FEES ENCLOSED =				\$ 791.00	
				Amount to be refunded:	\$
				charged	\$
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <input type="checkbox"/> A check in the amount of \$ _____ to cover the above fees is enclosed. <input checked="" type="checkbox"/> Please charge my Deposit Account No. <u>50-1407</u> in the amount of <u>\$ 791.00</u> to cover the above fees. A duplicate copy of this sheet is enclosed. <input type="checkbox"/> The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. <u>50-1407</u>. A duplicate copy of this sheet is enclosed. </div> <div style="width: 50%; font-size: 0.8em;"> NOTE: Where an appropriate time limit under 37CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status. SEND ALL CORRESPONDENCE TO: </div> </div>					
SOL SHEINBEIN G.E. EHRLICH (1995) LTD. C/O ANTONHY CASTORINA SUITE 207 2001 JEFFERSON DAVIS HIGHWAY ARLINGTON, VIRGINIA 22202, USA			<div style="text-align: center;"> </div> <div style="border-top: 1px solid black; margin-top: 5px;"> SOL SHEINBEIN NAME </div> <div style="border-top: 1px solid black; margin-top: 5px;"> 25.457 REGISTRATION NUMBER </div> <div style="border-top: 1px solid black; margin-top: 5px;"> May 21, 2001 DATE </div>		

INTERFERON GAMMA INDUCING FACTOR BASED VACCINE AND
USE OF SAME FOR PROTECTIVE IMMUNITY AGAINST MULTIPLE
SCLEROSIS

5 FIELD AND BACKGROUND OF THE INVENTION

The present invention relates to the treatment of multiple sclerosis and, more particularly, to interferon gamma inducing factor (IGIF) based vaccines for effecting same.

Based on their cytokine profile CD4⁺ T-cells can be divided to Th1
10 cells that produce large amounts of interferon gamma (IFN- γ) and TNF- α , and, to a much lesser extent, IL-4 and IL-10; Th2 cells that produce IL-4, IL-10, and IL-13 and, to a much lesser extent, IFN- γ and TNF- α (1-10), and the newly defined Th3 cells that produce significant amounts of transforming growth factor beta (TGF- β) and have been associated with oral
15 tolerance (11).

Th1 cells selected in response to various auto-antigens transfer T-cell mediated autoimmune diseases, whereas IL-4 secreting Th2 cells, selected in response to these same antigens, either inhibit or exert no profound effect on the inflammatory process (5, 12-24).

20 High levels of IFN- γ and low levels of IL-4 positively select for Th1 cells, whereas, low levels of IFN- γ together with high levels of IL-4 mediate Th2 selection (1-6).

Interferon gamma inducing factor (IGIF, interleukin-18, IL-18) is a recently described cytokine (25) that shares structural features with the interleukin-1 (IL-1) family of proteins (26). Activation of IGIF is mediated by interleukin-1 beta converting enzyme (ICE) (27, 28). Like IL-12, IGIF
25 is a potent inducer of the production of IFN- γ by Th1 and natural killer (NK) cells, and acts on Th1 cells together with IL-12 in a synergistic manner (25, 29-32).

30 Experimental autoimmune encephalomyelitis (EAE) is a T cell mediated autoimmune disease of the central nervous system (CNS) which, for many years and for a variety of experimental protocols, serves as a model for the human disease, multiple sclerosis (MS), a chronic degenerative disease marked by patchy destruction of the myelin that surrounds and insulates nerve fibers and mild to severe neural and muscular
35 impairments, since in both diseases circulating leukocytes penetrate the blood brain barrier and damage myelin resulting in impaired nerve conduction and paralysis (33, 34). Antigen specific T cells are thought to play a pivotal role in the manifestation of both diseases (35-37).